## REMARKS

In the Office Action dated December 12, 2005, the Examiner: (1) requests removal of the pages of the sequence listing filed in June of 2004; (2) rejects claims 2 – 5 and 19 under 35 U.S.C. § 112, ¶ 2; (3) rejects claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶1; and (4) rejects claims 1 – 6, 8, 19 and 21 – 37 under 35 U.S.C. § 112, ¶ 1. Applicants respond as follows:

**Response to Request to Remove Pages of the Sequence Listing**

The Examiner notes that Applicants have not requested removal of the pages corresponding to the sequence listing filed in June 2004. By the Amendment above, Applicants request removal of those pages.

**Response to Rejection of Claims 2 – 5 and 19 under 35 U.S.C. § 112, ¶2**

The Examiner rejects claims 2 – 5 and 19 under 35 U.S.C. § 112, ¶2 as being indefinite. Applicants have responded to this rejection by amending the claims. More precisely, Applicants have amended: (i) claim 2, by replacing the phrase "Formulas I-IX" with "Formulas I, II and IV – IX"; (ii) claims 2 and 19 to indicate that when Tm is less than or equal to 20°C, the value of $Tm_{20°C}$ is equal to zero (support may be found on page 32, lines 7 –9 of the specification as filed); and (iii) claim 2 by deleting the phrases that refer to circumstances in which the sense strand is only 18 bases in length. In view of these amendments, Applicants request that the pending rejection be withdrawn.

**Response to Rejections of Claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶1**

The Examiner rejects claims 1 – 6, 8 and 19 – 37 under 35 U.S.C. § 112, ¶1 for allegedly failing to comply with the enablement requirement. Applicants respectfully submit that the Examiner's rejection is an inappropriate application of the enablement requirement. The enablement requirement is met if the description permits practicing the invention without undue experimentation. *Johns Hopkins v. CellPro.* 152 F.3d 1342,

1361 (Fed. Cir. 1998). The Examiner has not shown what if any experimentation is necessary to practice the claims as amended.

The claims as amended are directed to methods and kits for selecting and using siRNA that have an increased likelihood of being functional and methods for developing an algorithm. (Only a few of the dependent claims add limitations that the siRNA have a defined level of functionality.) The steps of, for example, claim 1 as amended could easily be applied by persons of ordinary skill in the art after reading the disclosure, and from the rejection, it is unclear which step the Examiner believes that a person of ordinary skill would not be able to follow and for which undue experimentation would be necessary.

The Examiner includes a number of different reasons for issuing the rejection based on enablement. However, many of the reasons are directed to questions about sections of the specification and do not bear on the enablement of the claims. Thus, they are not pertinent to the inquiry of the patentability of the claims. In the interest of clarifying all of the issues raised by the Examiner, Applicants respond to each of those rejections as follows:

First, on pages 4 – 5 of the office action, the Examiner asserts that the claims are not enabled because a definition of the phrase rationally designed is not included in the text of the claims. Applicants respectfully disagree with the Examiner's position, but in the interest of furthering prosecution have amended claim 1 step (b) to include language that indicates that the at least one non-target specific criterion increases the likelihood that the candidate siRNA is functional. Accordingly, Applicants submit that this basis for the rejection is moot.

Second, beginning in the second full paragraph on page 5 of the office action, the Examiner asserts that the claims are not enabled because the methods do not recite a step wherein the results produced from the application of the non-target specific criterion are

correlated with the rationally designed siRNA. Applicants respectfully disagree with the Examiner's position, but in the interest of furthering prosecution have amended claim 1 step (c) to provide that the rationally designed siRNA satisfies at least one of the non-target specific criterion. Accordingly, Applicants submit that this basis for the rejection is moot.

Third, on pages 5 – 6 of the office action, the Examiner asserts that claim 2 does not satisfy the enablement requirement because there is no step for comparing the results of a formula to another siRNA or to an absolute standard. Applicants respectfully disagree with the Examiner's position, but in the interest of furthering prosecution have amended claim 2 to provide that the method requires the comparison of the results of a formula as applied to at least two siRNA and selecting the siRNA that has the higher score. Accordingly, Applicants submit that this basis for the rejection is moot.

Fourth, on pages 6 – 8 of the office action, the Examiner asserts that formulas I-IX and the criteria on pages 21 –22 do not appear to be a proven set of criteria. Applicants respectfully submit that the Examiner's concerns are not a proper basis for an enablement rejection. The Examiner appears to read into claim 2 the requirement of selecting a functional siRNA. However, claim 2 does not contain a limitation that the method selects a functional siRNA, only that the method can be used to select an siRNA from at least two candidates where the selected siRNA has an increased likelihood of being functional relative to another siRNA. Further, the Examiner's assertion that the formulas and the criteria on pages 21 –22 do not represent a proven set of criteria appears to be a misunderstanding of the invention and the enablement requirement as applied to the invention. Each of the individual criterion was determined and proven by bioinformatics techniques such as those described on pages 38 – 40 of the specification as filed. Although these criteria were established by bioinformatics techniques, patentability is not negated by the method of invention. 35 U.S.C. § 103 ("Patentability shall not be negatived by the manner in which the invention was made."). Thus, the enablement requirement does not require Applicants to recite the details of how each criterion was

determined or validated, only that the persons of ordinary skill can use the claimed criteria.

Fifth, on page 8 of the office action, the Examiner asserts that the claims are not enabled because the specification suggests the presence of certain undefined criteria embedded within the formulas VIII and IX that are not within Table IV, and that a skilled artisan is left to guess as to which parameter is the most essential parameter. Applicants respectfully submit that the enablement requirement does not mandate identification of which parameter is the most essential. Further, whether the criteria in formulas VIII and IX are also in Table IV is not relevant. All that is necessary is that the person of ordinary skill be able to follow the steps of the claimed method, and the Examiner has not show any reason why persons of ordinary skill would not be able to do so.

Sixth, on pages 8 – 9 of the office action, the Examiner asserts that the specification is confusing because of the description of how to select hyperfunctional siRNA. Applicants note that other than for pending claim 8, this section of the specification is not pertinent. Further, the section cited by the Examiner explicitly tells how to proceed with selecting hyperfunctional siRNA. Thus, to the extent that the Examiner asserts that the specification is non-enabling, Applicants respectfully submit that the application is not confusing. With respect to the Examiner's concern that the specification is internally inconsistent, Applicants note that the patent application provides nine formulas. Although the specification indicates that for formulas VIII and IX, a SMARTscore of higher than 0 or 20 effectively selected a set of functional siRNAs, the passage that is directed to selecting hyperfunctional siRNA is not limited to Formulas VIII and IX. Thus, *e.g.,* it may be advantageous when using the other formulas to begin with a lower SMARTscore, and a person of ordinary skill would understand this concept from the disclosure.

Seventh, on pages 9 –10 of the office action, the Examiner asserts that the claims are not enabled because Tm will yield either 0 or 100 in formulas VIII and IX, and the

difference in value can be so significant that it suggests that the invention cannot be practiced with the mere consideration of non-target specific criterion. Applicants submit that here the Examiner confuses a method for selecting a functional siRNA with a method for selecting a rationally designed siRNA, which is an siRNA that is more likely to be functional because of the criteria that has been applied. Further, as persons skilled in the art are aware, for a given set of candidate siRNA, if there is an inverted repeat of more than 4 base pairs within one candidate siRNA, *e.g.,* 6 base pairs in length, there will be at least 14 candidate siRNAs that will contain the inverted repeat. (The inverted repeat could begin at any one of positions 1 – 14.) All of those 14 candidate siRNAs would have the same Tm value. However, using the non-target specific criteria that examine whether a particular base is present or absent at a particular site, one will be able to increase the likelihood of distinguishing the relative functionality of the candidate siRNAs. Further, for some genes, there may be no inverted repeats that are longer than 4 base pairs. Thus, although when selecting a rationally designed siRNA it may be the case that the presence or absence of inverted repeats is significant, it may not be of use in distinguishing the relative functionality among different candidate siRNAs.

Eighth, on the top of page 10 of the office action, the Examiner asserts that the use of the phrase "sense strand" in the recited claims is not limited to the sense strand of the respective candidate siRNA. Applicants have amended the claims to address this issue.

Ninth, in the full paragraph on page 10 of the office action, the Examiner asserts that for selecting functional and hyperfunctional siRNA a skilled artisan would need to resort to unpredictable *de novo* experimentation without particular guidance from the specification. However, Applicants again note that most of the pending claims are directed to methods for selecting siRNA that have an increased likelihood of being functional, not for selecting functional siRNA. Absent direction as to which portion of each claim is not enabled the rejection is improper. Moreover, Applicants have specified that to assist in finding functional siRNA, a person of ordinary skill should look to a

higher SMARTscore according to the formulas, and a person of ordinary skill would understand that her best option is to start with the highest SMARTscore for all possible siRNA. Further, any *in vitro* validation that a person of ordinary skill might want to use would be routine and not require undue experimentation.

Tenth, on pages 10 to 12 of the office action, the Examiner rejects claims 3 – 5 for not being limited to *in vitro* applications. Applicants have amended the claims to include this limitation. Accordingly, Applicants request that the rejection being withdrawn.

**Response to Rejection of claims 1 – 6, 8 and 21 – 37**

The Examiner rejects claim 1 – 6, 8 and 21 – 37 as allegedly failing to comply with the written description requirement. Applicants respond as follows:

First, the Examiner reiterates her rejection of claim 19, asserting that it encompasses siRNA to targets not disclosed in the specification as filed, and undiscovered targets such that further experimentation would be required to optimize two separate siRNA molecules for the undiscovered target genes, their polymorphic and allelic variants of the target genes. Applicants have made explicit what was previously implicit in claim 19, the first and second optimized siRNAs have the two highest scores for application of any one of the recited formulas. Support for this amendment may for example be found on page 33, lines 11 – 18 of the specification as originally filed.

Contrary to the Examiner's assertion, the claim requires no experimentation. A person of ordinary skill can simply apply any one of the formulas to any target sequence, and identify the two sequences of 18 – 25 bases that have the highest scores when using a particular formula and form a kit. There is no guesswork and the contents of the kit would be readily apparent to a person of ordinary skill in the art. Further, the claim does not specify a particular level of functionality that results from using the first and second

optimized siRNA, and as the Examiner has repeatedly noted in the Office Action, the formulas may be used for the relative values that are generated.

Moreover, the provision of the MPEP that the Examiner cites suggests that Applicants have complied with the written description requirement. It requires a known correlation between the structure and function. Applicants have provided this information through its bioinformatics analysis.

As the Court of Appeals for the Federal Circuit has emphasized: "the written description requirement does not dictate that claims to nucleotide sequences can only be made by reciting the precise sequences." *Capon v. Eshhar,* 418 F.3d 1349, 1358 (Fed. Cir. 2005); *see also Monsanto v. Scruggs,* 342 F. Supp. 2d 584, 601 (D. Miss. 2004) ("Publication of the specific gene sequences for each possible embodiment of the claimed inventions was simply unnecessary."). Claim 19 is directed to a kit of the two siRNA most likely to be of the highest functionality as defined by any one particular formulas. Thus, although the precise sequences of the siRNA within any one kit will be determined based on the target, the scope of the claim is nonetheless readily apparent to a person of ordinary skill.

Second, on pages 14 –15, the Examiner asserts that claim 1 and all claims dependent thereon are rejected under the written description requirement because the application does not delineate a finite set of what a proven set of criteria are that enhance the probability of identifying functional or hyperfunctional siRNA. Applicants agree that the application does not delineate all possible criteria. However, the invention to which claim 1 (as well as a number of the claims that depend on it) is not limited to the use of a particular criteria but to the methods of using non-target specific criteria in general. Both the idea to use these non-target specific criteria, and specific criteria delineated in the specification are inventive, and Applicants have adequately described both aspects of the application by providing a plurality of different criteria that may be used. Thus, they have provided a written description of the invention of using non-target specific criteria

to increase the likelihood of increased functionality (*e.g.*, claim 1 and the claims that depend on it), as well as written description for specific criteria such as those embodied (*e.g.*, claim 2 as the claims that depend on it).

Finally, Applicants note that claims 6 and 27 – 29 do not depend on claim 1, and it is unclear from the Office Action whether the Examiner appreciated this fact when making the rejections.

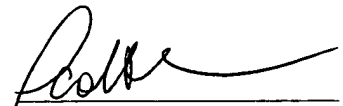
**Conclusion**

All of the Examiner's rejections having been fully traversed and addressed, Applicants respectfully request allowance of the pending claims.

Applicants submit no fee is required in connection with the filing of this Amendment and Reply. If any fee is deemed necessary, please charge Deposit Account No. 11-0171.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,



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